Serum cytokines and increased total serum IgE in alcoholics

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Background: It has been reported that total serum IgE is increased in alcohol abusers, but the mechanisms responsible are not known. Production of IgE depends on B-cell stimulation by both antigens and some cytokines, particularly IL-4 and IL-13. Chronic alcoholism and alcoholic liver disease are accompanied by changes in cytokine production.

Aim of the study: To evaluate if IgE increase in alcoholics could be associated to a ethanol-induced imbalance of the cytokine profile.

Patients and methods: A total of 65 patients (53 males and 12 females, aged 47 ± 12 years), admitted to the hospital because of ethanol abstinence symptoms entered the study. On admission, total serum IgE was measured by chemiluminescent EIA and serum IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, and interferon-gamma were measured by ELISA. Data were compared with those of 40 healthy control subjects.

Results: Serum IgE, IL-6, IL-8, IL-10, IL-12, and IL-13 were found to be high in alcoholic patients compared with healthy volunteers. Some parallelism was observed between serum IgE and both serum IL-10 and IL-13 were increased in alcoholics.

Conclusions: Total serum IgE elevation in alcoholics with abstinence syndrome is accompanied by an increase of some type 2 cytokines. Ethanol-induced alterations in the cytokine profile may contribute to increased IgE levels in alcoholics.

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INTRODUCTION

Several studies have reported that total serum IgE is increased in alcoholic liver cirrhosis.[1–6] It was initially suggested that advanced liver injury was the cause of IgE elevation[2] as it occurs with other immunoglobulins, as a component of the well-known hypergammaglobulinemia of chronic liver disease. It was later observed that serum IgE is only increased in patients with alcoholic cirrhosis when compared with cases with liver cirrhosis due to other factors,[6] thus suggesting that a specific feature of patients with alcoholic liver disease was the cause of IgE elevation. It has also been reported that increased total serum IgE alcoholics is not related to liver function,[6,7] and that IgE is increased in serum of alcohol abusers regardless of the degree of histologic liver damage.[8] Furthermore, it was observed that serum IgE in alcoholics descends shortly after ethanol abstinence.[3,6,7] All these reports suggest that chronic ethanol ingestion per se may play a role in IgE increase. It has been similarly demonstrated that alcohol is an independent factor for IgE elevation in patients with HIV-1 infection.[9] Likewise, it was shown that ethanol-related IgE increase is independent of associated habits such as smoking, both in alcoholics[8] and in a defined healthy population.[10] Finally, it has been reported that children of mothers who abuse alcohol have higher cord blood IgE concentrations.[11]

Alcoholics and alcohol abusers therefore tend to have higher levels of total serum IgE, but the cause of this phenomenon remains unknown. It is well-known that some cytokines are clearly involved in IgE production. The so-called type 2 cytokines (IL-5, IL-10 and, particularly, IL-4 and IL-13)[12–18] increase IgE synthesis. Interleukin-6 may also potentiate IgE synthesis.[17,19,20] Conversely, type 1 cytokines (particularly IFN-gamma) inhibit IgE synthesis.[17,18] Interleukin-12 has the same effect through stimulation of interferon-gamma production[17,21] and IL-8 has also some inhibitory effects on IgE synthesis.[22,23] It is also known that ethanol induces profound changes in some serum cytokines.[24–36] The present study was designed to test the hypothesis that IgE increase in alcoholics could be due to an ethanol-induced imbalance of such cytokines, analyzing their serum levels.

PATIENTS AND METHODS

Patients

A total of 65 patients (12 females and 53 males), aged 47 ± 12 years (range 30 to 78) entered the study. All were chronic alcohol abusers, with an average daily alcohol intake of more than 120 g for a minimum of 5 years. All were admitted to the hospital because of ethanol withdrawal symptoms. Patients had stopped drinking 24 to 48 hours before admission, due to their own decision or on medical advice. After the abstinence symptoms had subsided, all included patients denied a present or past history of allergic diseases. A total of 28 cases (43%) were current smokers. Other causes of IgE increase[37] were not evident in their clinical records. Forty healthy volunteers, aged 22 to 60 years, served as controls. Alcohol intake was lower than 30 g/wk in all of them. Fifteen controls (39%) were smokers.

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Methods

The study was approved by the Ethics Committee of the Hospital. Samples of sera were taken during the first 24 hours of hospital stay and stored at −80°C until tested. Total serum IgE was measured by a chemiluminescent enzyme immunoassay (Immulite, Diagnostic Products Corporation, Los Angeles, USA). Serum IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, and interferon-gamma were measured using a commercially available ELISA (Quantikine, R&D Systems, Minneapolis, USA). Original reagents were used, and the manufacturer's instructions were followed in all cases. The lower detection limit for total serum IgE was 2 IU/mL. In the light of previous experience, IgE values higher than 170 IU/mL were considered elevated. This figure approximates the 75th percentile in a healthy population.[8] The lower detection thresholds for IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13 and gamma-interferon were 4.1 pg/mL, 3.0 pg/mL, 0.7 pg/mL, 10 pg/mL, 2 pg/mL, 5 pg/mL, 32 pg/mL, and 3 pg/mL, respectively. Blood cell counts were obtained on admission in a Technicon H3 System (Bayer Diagnostics, Germany). Routine serum biochemical parameters (albumin, cholesterol) were assayed in a Hitachi 747 autoanalyzer (Boehringer-Mannheim, Germany).

Statistical Analysis

Data were processed in an SPSS (SPSS Inc., USA) statistical package. The Chi-square test was used to compare dichotomous variables. The two-tailed Mann-Whitney test were used to compare continuous variables, since most of them did not fullfil criteria of normality. For the same reason, Spearman's rank test was employed for bivariate correlation. In order to assess the effects of potential confounding variables, a multiple logistic regression model was developed. These variables were made to enter the model and estimated odds ratios and 95% confidence intervals were calculated from the coefficients. For statistical analysis, values below the aforementioned levels of detection of serum cytokines were considered as zero. A P value of less than .05 was considered statistically significant.

RESULTS

Total Serum IgE

In the group of alcoholics, median serum IgE was 134 IU/mL (geometric mean 148 IU/mL, range 15.8 to 2555 IU/mL). In controls, median IgE was 35 IU/ml (geometric mean 37 IU/ml, range 4–437 IU/ml) ($P < .0001$). A total of 28 alcoholic patients (43%) had elevated serum IgE levels (>170 IU/mL), compared with only 6 controls (15%) ($P = .002$). Individual values are depicted in Figure 1.

Serum Cytokines

Interleukin-4 and IL-5 were below the level of detection in all serum samples assayed of both cases and controls. Interferon-gamma was detected in serum of only 6 (9%) alcoholic patients (range 3.4 to 21.2 pg/mL) and none of the controls (P = NS). Levels of serum IL-6, IL-8, IL-10, IL-12, and IL-13 were significantly increased in alcoholics with respect to controls (Fig 1).

Relationship of Serum Cytokine Levels with Increased IgE in the Group of Alcoholics

Table 1 represents a comparison of serum cytokines between patients with normal (<170 IU/mL) or high (>170 IU/mL) serum IgE values. Serum IL-13 was higher in cases with high IgE levels. Serum IL-10 also tended to be higher in in cases with increased IgE levels, but without statistical signification. Likewise, a weak positive but significant correlation was observed between serum IL-13 and IgE (Table 2, Fig 2). Serum IgE was higher in cases with IL-10 values higher than the median (10.9 pg/mL) than in cases with IL-10 values below that figure (216 IU/mL versus 98.6 IU/mL, $P = .035$). Spearman's correlation between IgE and IL-10 was not significant with this sample size. Similarly, no significant correlation could be demonstrated between IgE and the other cytokines assayed (Table 2).

Potential Confounding Factors for IgE Increase in the Group of Alcoholics

Parasitic Infestation

Peripheral blood eosinophilia, a surrogate marker of parasitic infestation, was absent in all cases. Median eosinophil count in alcoholics was 62/mm^3 (range 0 to 336/mm^3). No correlation was observed between eosinophil count and total serum IgE (r: −0.10, P NS).

Malnutrition

No significant correlation was observed between serum albumin or serum cholesterol (both dependent on liver function but also markers of nutrition) and total serum IgE levels (r: −0.02, P NS; and r: 0.11 P NS, respectively). Mean serum albumin level in alcoholics was 3.8 ± 0.7 g/dL. Mean serum cholesterol level in alcoholics was 190 ± 66 mg/dL.

Liver Disfunction

Liver function was rather preserved in most patients. Fifty-three alcoholics (82%) had a prothrombin (Quick's) index higher than 75%. Median serum IgE was 164 IU/mL (range 15.8 to 2555 IU/mL) in these cases, and 96.8 IU/mL (range 16 to 1151 IU/mL) in the remaining 12 patients with lower prothrombin values (P NS). Serum IL-8 values were higher in the group of patients with poorer liver function (median 154 pg/mL and range 10.7–2800 pg/mL, versus median 24.2 pg/mL and range <10–952 pg/mL, $P = .004$). Levels of the rest of the cytokines were not significantly different between the two groups of patients. Parameters of liver function were similar in alcoholics with either increased or normal IgE values (Table 1).

Smoking

Median serum IgE tended to be higher in alcoholic smokers than in alcoholic non-smokers, but the difference was not significant (Table 3). When cases and controls were included in a multivariate logistic regression analysis, alcohol abuse (but not smoking habit)

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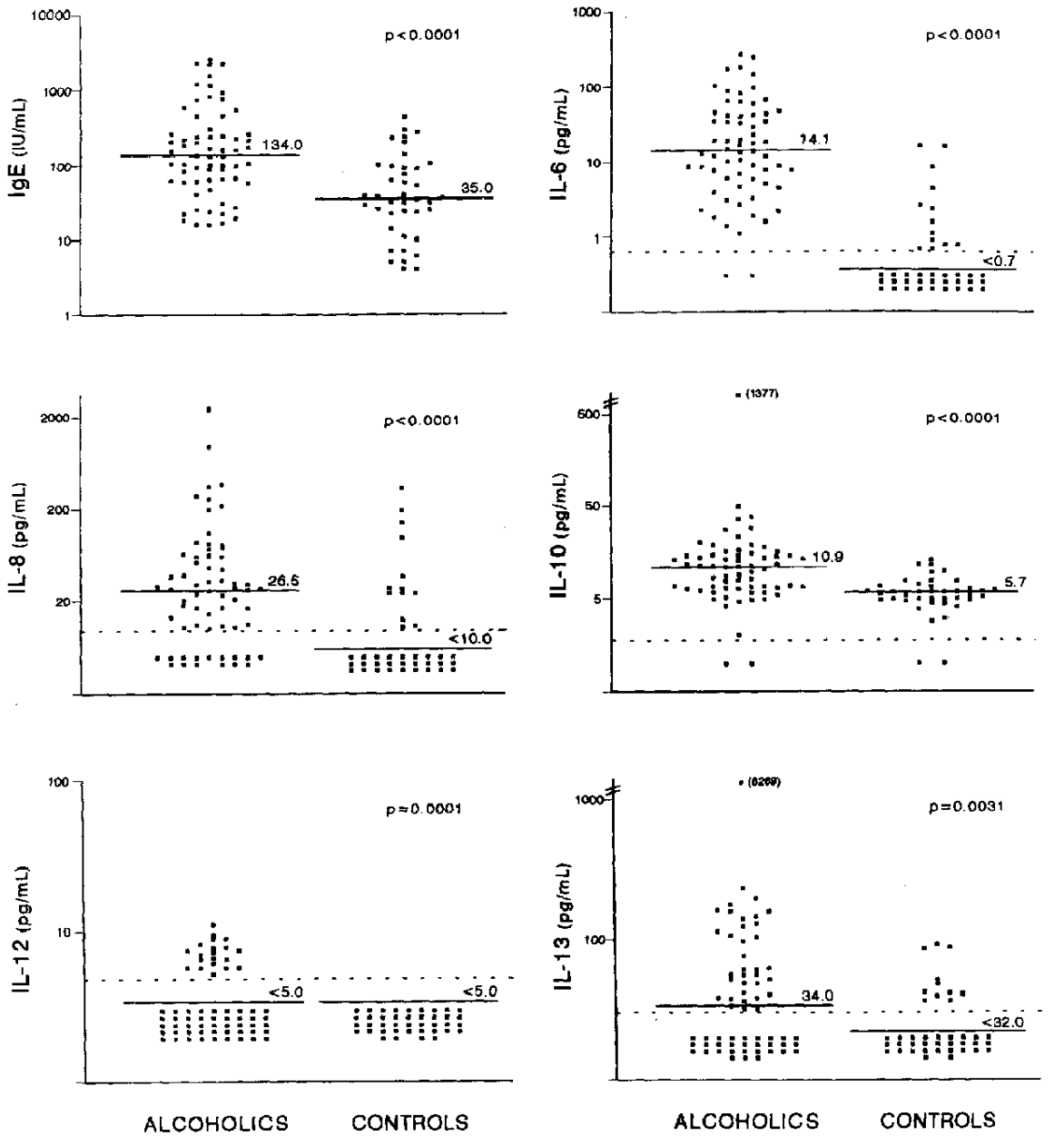

Figure 1. Serum concentrations of IgE, IL-6, IL-8, IL-10, IL-12, and IL-13 in alcoholic patients and healthy controls. The dashed line represents the lower level of detection of the method used. Horizontal solid lines represent median values.

was associated with increased (>170 IU/mL) IgE levels (OR 4.2, 95% CI 1.5–11.6, $P = .004$; and OR 2.0, 95% CI 0.8 to 4.9, P NS, respectively). Serum IL-10 and IL-12 levels were higher in alcoholic smokers than in alcoholic non-smokers (Table 3). Similarly, in healthy controls, IL-10 was higher in smokers than in non-smokers (median 6.1 pg/mL and range 4.9 to 11.3 pg/mL; versus median <2 pg/mL and range <2 to 12.9 pg/mL, $P = .025$). Multivariate logistic regression analysis showed that both alcohol abuse and smoking habit were associated with increased (>10.9 pg/mL) serum IL-10 values (OR 12.2, 95% CI 3.3–47.9, $P = .0002$; and OR 3.4, 95%

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CI 1.3–8.6, $P = .011$, respectively). No more significant differences in serum cytokine levels between smokers and non-smokers were observed.

DISCUSSION

Our results confirm previous reports[1–10,38,39] of increased serum IgE levels in alcoholics compared with healthy controls, and showed a parallel elevation of some serum cytokines. Alcoholic patients with abstinence syndrome were chosen for this study because they constitute an homogeneous group as they are heavy drinkers (of more than 150 g/day),[40] who maintained their alcohol intake up to a few hours before admission. In previous reports it was observed that the amount of IgE increase in these patients is similar to that of other subgroups of alcoholics.[6] In the present study, observed values were also similar to those of former reports, with median IgE levels of 134 IU/mL, far above those of the normal non-alcoholic population, 43% of alcoholics having high (>170 IU/mL) IgE values. To our knowledge, no increase in allergic diseases have been reported in alcohol abusers. In this study atopy was excluded by clinical history in both patients and controls. This has some limitations, perhaps more in alcoholic patients who may not be entirely reliable, although previous studies have shown that total serum IgE is increased in both atopic and non-atopic alcoholics.[7] IgE increase in alcohol abusers does not seem to be due to associated confounding factors, such as parasitic infestation, smoking, malnutrition or liver disfunction. Elevated total serum IgE levels in alcohol abusers or patients with alcoholic liver disease have been reported uniformly worldwide in Norway,[39] Sweden,[7] Italy,[5] Spain,[6,8] the USA,[2,3] Puerto Rico,[10] Israel,[4] and Australia.[38] This fact, and the absence of associated peripheral blood eosinophilia, makes it improbable that a parasite is the cause of increased total serum IgE in all alcoholics. Smoking is frequent in alcoholics and is a cause of IgE elevation.[41] Previous and present studies have shown that the IgE increase related to chronic alcohol intake is independent of smoking.[8,10] Malnutrition is also a cause of serum IgE elevation[42] and is also common in alcoholics. The fact that poor nutrition plays a role in IgE increase of alcoholics cannot be ruled out; however, no relationship was observed between IgE elevation and serum albumin levels in alcoholics of this or prior studies.[6,8] Finally, data of liver function were not correlated with IgE increase in alcohol abusers, as previously reported.[6,8] The influence of the amount of alcohol intake on IgE levels could not be investigated because all patients were heavy alcohol abusers, as already mentioned. Biochemical data of alcohol consumption (serum GGT, mean corpuscular volume) were similar in patients with increased and non-increased total serum IgE.

Together with total serum IgE increase, an increase in serum IL-6, IL-8, IL-10, IL-12, and IL-13 was observed in alcoholics. Elevation of serum IL-6, IL-8, and IL-10 was particularly significant. Increased levels of serum IL-6 and IL-8 in patients with alcoholic liver disease have been previously reported, the latter more marked during alcoholic hepatitis.[24,26–29,31–33] In vitro, PBMNC of alcoholics tend to produce more IL-6 and IL-8 than healthy controls.[34] It is also known that ethanol can increase human monocyte IL-10 production.[35] To our knowledge, elevated serum levels of IL-10, IL-12, and IL-13 in alcoholics have not been reported up to now. Of all these cytokines, IL-13 is clearly implicated in IgE synthesis[14–18] and IL-6 can also potentiate IgE production.[19,20] Interleukin-8 has negative effects on IgE synthesis.[22,23] Interleukin-12 suppresses the synthesis of IgE by human PBMNC[21] and directs the differentiation of naive T lymphocytes in a Th1 direction in vitro.[43] In some murine models, however, IL-12 can exacerbate rather than suppress Th2-dependent phenomena in the absence of IFN-gamma,[44] and some doses may even enhance the synthesis of antigen-specific IgE.[45] Interleukin-10 is considered as a type 2 cytokine with stimulating activity on B cell function.[18,46] With respect to IgE synthesis, it has been reported both that it accelerates IgE production by anti-CD40 and IL-4 stimulated PBMNC by enhancing IL-6 production through the activation of T lymphocytes,[47] and that it prevents IL-4-induced IgE synthesis by inhibiting the accessory cell function of monocytes.[48] With the method used in

Table 1. Serum Cytokine Levels and Markers of Alcohol Consumption in Alcoholic Patients with Either Normal (<170 IU/mL) or High (>170 IU/mL) Serum IgE Values*

	IgE < 170 IU/mL (n = 37)	IgE > 170 IU/mL (n = 28)	P Value
Serum cytokines			
IL-6 (pg/mL)	16.8 (1.1–253)	12.6 (<0.7–272)	NS
IL-8 (pg/mL)	26.9 (<10–372)	24.4 (<10–2800)	NS
IL-10 (pg/mL)	8.3 (<2–49.9)	13.3 (<2–1377)	NS
IL-12 (pg/mL)	<5 (<5–9.4)	<5 (<5–11)	NS
IL-13 (pg/mL)	<32 (<32–6269)	54.6 (<32–231)	.004
Liver function tests			
Serum albumin (g/dL)	3.7 (2.2–4.8)	4.0 (2.3–5.8)	NS
Serum bilirubin (mg/dL)	1.2 (0.3–15.9)	1.0 (0.4–11.7)	NS
Prothrombin index (%)	97 (20–100)	99 (39–100)	NS
Serum AST (IU/mL)†	60 (11–226)	48 (15–282)	NS
Serum ALT (IU/mL)	35 (11–182)	39 (15–248)	NS
Markers of alcohol consumption			
Erythrocyte MCV (fl)‡	99 (89–113)	100 (89–118)	NS
Serum GGT (IU/mL)†	155 (14–3850)	183 (23–1236)	NS

* Data are represented as median and (range).
† Normal upper limits: sAST 28 IU/mL, sALT 29 IU/mL, and sGGT 32 IU/mL.
‡ MCV: mean corpuscular volume.

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Table 2. Correlation Between Serum IgE Values and Serum Cytokine Levels in the Group of Alcoholics

	IL-6	IL-8	IL-10	IL-12	IL-13
Spearman correlation coefficient IgE/cytokine	.007	−.046	.210	.109	0.301*

*$P = .015$.

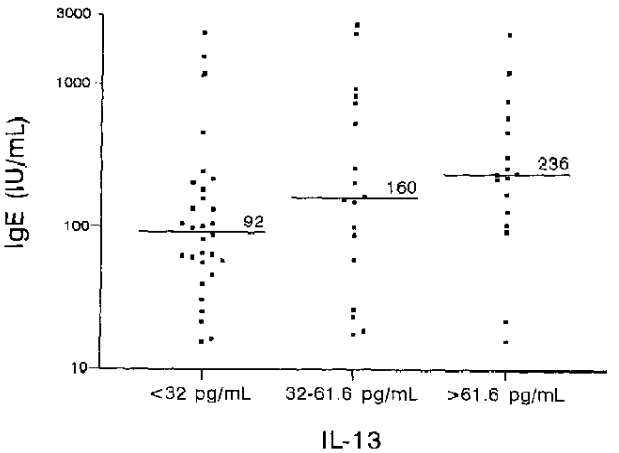

Figure 2. Correlation between total serum IgE and IL-13 in the group of alcoholics. Patients were ranked according IL-13 levels: 32 pg/mL and 61.6 pg/mL represent the lower level of detection and the median level in detectable cases, respectively.

Table 3. Serum Total IgE and Cytokine Levels in Alcoholic Smokers and Alcoholic Non-smokers*

	Smokers (n = 28)	Non-smokers (n = 37)	P Value
Total serum IgE (IU/mL)	209.5 (16–1531)	103 (15.8–2555)	NS
Serum cytokines			
IL-6 (pg/mL)	26.6 (<0.7–253)	10.3 (<0.7–272)	NS
IL-8 (pg/mL)	26.3 (<10–952)	26.5 (≤10–2800)	NS
IL-10 (pg/mL)	13.3 (<2–1377)	7.8 (<2–49.9)	0.045
IL-12 (pg/mL)	2.9 (<5–9.4)	<5 (<5–11)	0.003
IL-13 (pg/mL)	38.4 (<32–195)	54.6 (<32–6269)	NS

* Data are represented as median and (range).

the present study, no alterations could be observed either in serum IL-4 and IL-5 (two characteristic type 2 cytokines) or interferon-gamma (the most important type 1 cytokine).

In patients with alcoholic liver disease, it has been suggested that increased IL-6 is responsible for elevated serum IgA values.[24,30,36] We also hypothesize that the observed alterations in the cytokine network could result in a net increase of IgE synthesis by B cells. A similar mechanism for total serum IgE elevation has been suggested both in patients with HIV infection[49,50] and in smokers.[51,52] Along this line, an increase in IL-10 levels in both alcoholic and non-alcoholic smokers was incidentally observed in the present study. According to our results, the strongest statistical relation with total serum IgE elevation in alcoholics is observed with IL-10 and IL-13 increase, particularly the latter. Interleukin-13 is a T-cell derived cytokine which seems to be very important for IgE synthesis. The spectrum of biologic activities of IL-13 largely overlaps those previously ascribed to IL-4. Class switching of B cells to IgE is induced by IL-4 and IL-13.[14–18] In fact, IL-4 and IL-13 may have a common component in their receptors and similar signaling pathways.[53] Interleukin-13 overproduction in alcoholics may therefore contribute to elevated serum IgE levels in these patients. Prior IL-4 production is necessary for IL-13 synthesis, but IL-4 presence tends to be early and transient.[17,18] Alterations in IL-4 production in alcoholics cannot be excluded from our data, as its action may be only paracrine, with no reflection on serum levels.

In summary, in this observational study in alcoholics we have observed a parallel increase of total serum IgE and some cytokines involved in IgE synthesis, particularly IL-10 and IL-13. When writing about cytokines, is difficult to draw any conclusion because of the confounding variety of both cell sources and the range of biologic activities of each cytokine.[17] Also, as previously mentioned, serum cytokine levels can offer only an indirect measurement of these networks at the cellular milieu. Experimental in vitro studies are therefore needed both to determine the elevation mechanisms of these serum interleukins in alcohol abusers, as well as to confirm that this imbalance in the cytokine profile is responsible for increased total serum IgE in alcoholics.

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